Docket No. ORT-1548

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	SCHULTZ, T. et al.
Serial No.	:	10/022,138
Filed	:	December 13, 2001
Title	:	Steroid Hormone Products and Methods for Preparing Them
Art Unit	:	1612
Examiner	:	Qazi, S.

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8/24/09
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Yuriy P. Stercho
(Name of applicant, assignee, or Registered Representative)

/Yuriy P. Stercho/
(Signature)

8/24/09
(Date of Signature)

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

Dear Sir:

This is a reply to the Examiner's Answer, dated June 23, 2009 in an appeal from the Final Rejection of August 21, 2008, a Notice of Appeal having been received by the USPTO on December 16, 2008. Appellants' Reply Brief is being submitted on August 24, 2009.

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REAL PARTY IN INTEREST

The real party in interest of the above-referenced patent application is Ortho-McNeil Pharmaceutical, Inc., the assignee of record, having a principal place of business at Route 202, Raritan, NJ 08869.

RELATED APPEALS AND INTERFERENCES

A prior appeal was filed in the above-referenced application on January 20, 2004, Appellants having filed a Notice of Appeal on that date. Appellants filed an Appeal Brief in the prior appeal on March 22, 2004. In response to that Appeal Brief, the Examiner mailed a Non-Final Rejection on June 29, 2004, withdrawing the Final Rejection mailed October 21, 2003. A copy of that Non-Final Rejection is already part of the record of this application.

A second prior appeal was filed in the above-referenced application on July 27, 2005, Appellants having filed a Notice of Appeal on that date. Appellants filed an Appeal Brief in the second prior appeal on September 27, 2005. In response to that Appeal Brief, the Examiner mailed a Non-Final Rejection on May 4, 2006, withdrawing the Final Rejection mailed March 15, 2005. A copy of that Non-Final Rejection is already part of the record of this application.

A third prior appeal was filed in the above-referenced application on July 16, 2007, Appellants having filed a Notice of Appeal on that date. Appellants did not file an Appeal Brief in the third prior appeal but, instead, filed a Request for Continued Examination on October 16, 2007.

STATUS OF CLAIMS

Claims 1, 6 and 7 are pending in this application and are the subject of this Appeal. Claims 1, 6 and 7 stand rejected.

Claims 2-5 and 8 have previously been cancelled, and claims 9-17 have previously been withdrawn.

STATUS OF AMENDMENTS

The claims stand amended as set forth in the Response To Office Action filed on April 23, 2008.

No claim amendments were filed subsequent to the mailing of the Final Rejection on August 21, 2008.

SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is the only independent claim in this application. Claim 1 defines a steroid hormone product having an improved dissolution profile and release rate profile. The product comprises norgestimate in admixture with lactose. Substantially all of the norgestimate is in non-crystalline form, and it is stabilized in this form by the lactose. The hormone products taught by the invention are characterized by highly favorable dissolution properties. See, e.g., page 4, lines 16-21 of the specification.

Stabilization of the steroid hormone norgestimate in the high-energy amorphous form by lactose is described at page 9, line 25 to page 10, line 6 of the specification. The superior dissolution rate of the high-energy amorphous form of norgestimate, as compared to the lower energy crystalline form, is shown by the data in Table 1 at page 10 of the specification. The improvement in dissolution rate for the amorphous form of norgestimate, subsequent to co-milling with lactose, as compared to the lower energy crystalline form of norgestimate co-milled with lactose, is shown by the data in Tables 2 and 3 at, respectively, pages 11 and 12 of the specification.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1, 6 and 7 are obvious over US Patent No. 5, 858,405 (Gast), in view of Morita, the Merck Index, Jain, et al., Sebhatu, et al., Rialker et al. and Bouckton et al.

Whether claims 1, 6 and 7 are obvious over EP 0503521 and the Merck Index.

ARGUMENT

First Rejection: Claims 1, 6 and 7 are Obvious over US Patent No. 5, 858,405 (Gast), in View of Morita, the Merck Index, Jain, et al., Sebhatu, et al., Rialker et al. and Bouckton et al.

As the Examiner has acknowledged, Gast teaches a hormonal product wherein the excipient is in crystalline or non-crystalline form. There is no teaching or suggestion in Gast of such a product wherein the steroid hormone is in non-crystalline form, as required by the claimed invention. Morita also relates only to the lactose excipient, noting that lactose has been widely used in pharmaceutical preparations and that several grades are available, including non-crystalline lactose. Morita says nothing about a hormonal product wherein a steroid hormone is in non-crystalline form. Jain merely states that a hydrophobic drug may stabilized in the presence of hydrous and anhydrous lactose. Sebhatu et al, Rialkaret al, and Bouckton et al likewise relate only to the use of lactose in pharmaceutical preparations. As to Merck, the Examiner ascribes to this reference the teaching that estrone is in non-crystalline form based on the statement in Merck that estrone can be crystalline. Even assuming that this is true, the reference still fails to teach or suggest a hormonal product which includes the steroid hormone norgestimate, wherein norgestimate is in non-crystalline form and is stabilized in this form by lactose.

The criticality of the norgestimate being in non-crystalline form is clearly set forth in the specification. Appellants direct the Board to page 6, lines 15-23 of the specification wherein it is noted that steroid hormones can exist in various solid state forms and that the particular solid state form may significantly affect properties such as dissolution rate and physical/chemical stability. It is further noted in that section of the specification that the higher energy, non-crystalline solid-state form will exhibit an increase in dissolution rate

over the more stable, lower energy crystalline form. Appellants also noted page 7, line 30 to page 8, line 2, wherein it is stated that in the manufacture of steroid hormone products it would be highly desirable to increase the dissolution rate of the hormone while at the same time either improving or at least not reducing the physical/chemical stability of the hormone.

These objectives are achieved by the claimed invention, as shown by the data set forth in Tables 1-4. In particular, the data in Table 1 demonstrate the difference in dissolution rates for non-crystalline norgestimate as compared to the lower-energy crystalline form. Note that the dissolution rate for amorphous norgestimate at 60 minutes is about the same as the lower energy crystalline form at 120 minutes and that the dissolution rate for the amorphous form at 120 minutes is significantly higher than the rate for the crystalline form at 140 minutes. The data in Tables 2 and 3 illustrates the effect on dissolution rate as norgestimate begins to re-crystallize from the higher energy amorphous form. As shown by these data, the dissolution rate of norgestimate decreases as the steroid converts to the lower energy crystalline form. The data in Table 4 show that the dissolution properties of norgestimate are not only dependent on storage conditions, but also on the mixing energetics imparted during the manufacturing process. Note that as energy is imparted over time and higher levels of amorphous norgestimate are present, the dissolution characteristics improve even when storage is unprotected under accelerated conditions.

As stated in the specification at page 13, lines 11-22, taken together the data from these studies demonstrate that when a mixture of an excipient and a steroid active ingredient is subjected to sufficient mechanical energy, the excipient and the steroid active ingredient form a less crystalline, more highly energetic composition. Furthermore, under appropriate mixing conditions, the lactose component stabilizes the steroid in a highly energetic, substantially non-crystalline state, thus preventing

recrystallization of the steroid. The highly energetic, non-crystalline steroid active ingredient dissolves more readily and is better able to maintain desirable dissolution characteristics under a variety of conditions of ambient humidity and ambient temperature.

The portions of the specification cited above establish the criticality of the non-crystalline steroid hormone and the unexpected results that derive from this form of the hormone. Where, as here, the specification contains specific data indicating substantially improved properties, unexpected results are established, absent evidence to the contrary. In re Soni, 34 USPQ 2d 1684, 1687-88 (Fed. Cir. 1995).

The Examiner states that "[n]o criticality of invention was noted in the claims". *Examiner's Answer* at 8. Appellants respectfully reply that criticality is reflected in the claims by the terms " having improved dissolution and release rate properties" and "wherein substantially all of said norgestimate is in non-crystalline form and wherein said lactose stabilizes said norgestimate in its non-crystalline form", such terms being supported by the data in the specification as originally filed and discussed herein above.

The Examiner states that Appellants argued the references separately and did not address the combination of references. *Examiner's Answer* at 7. Appellants respectfully assert that the Examiner has failed to show how the cited references teach or suggest the claimed product " having improved dissolution and release rate properties" and "wherein substantially all of said norgestimate is in non-crystalline form and wherein said lactose stabilizes said norgestimate in its non-crystalline form", whether read singly or in combination.

Second Rejection: Claims 1, 6 and 7 are Obvious Over EP 0503521 and the Merck Index

The Merck reference has been discussed above. There is no direct teaching in this reference that the steroid estrone can exist in non-crystalline form. One must assume this from the statement in Merck that estrone can be crystalline. Even making this assumption, the reference still fails to teach or suggest a hormonal product that includes the steroid hormone norgestimate, wherein norgestimate is in non-crystalline form and is stabilized in this form by lactose.

As to EP '521, this reference discloses a process for dry mixing steroidal agents and excipients to provide a "rugged" or "robust" content uniformity. The reference defines this to mean that the resulting mixture has fewer areas where there is too much or too little of the steroid. This is accomplished by selecting excipients, such as spray-dried polyalchohols, granulated α-lactose and mixtures thereof. According to the reference, these excipients are selected because they have a high binding affinity and low demixing potential for the disclosed steroidal agents. EP '521 fails to teach or even make any suggestion regarding a product comprising norgestimate in admixture with lactose, wherein substantially all of the norgestimate is in non-crystalline form and wherein the lactose stabilizes the norgestimate in this form.

The Supreme Court, in KSR International Co. v. Telefelex, Inc., 82 U.S.P.Q. 2d 1385 (2007), stated that while the obviousness analysis need not seek out precise teachings in the prior art directed to the subject matter of the claimed invention, obviousness rejections cannot be based on "mere conclusory statements." Instead, "some articulated reasoning with some rational underpinning" must be provided to support an obviousness rejection. The Examiner fails to provide such reasoning and underpinning. The only manner in which the claimed product could be derived from either Merck or EP '521 is by applying

Appellant's own teachings to these disclosures. Such hindsight reconstruction of the invention based on reading Appellants' own teachings into the prior art is clearly impermissible. In re Dembiczak, 50 USPQ 2d 1614, 1617 (Fed. Cir. 1999).

The Examiner again states that Appellants argued the references separately and did not address the combination of references. *Examiner's Answer* at 9. Appellants respectfully assert that the Examiner has failed to show how the cited references teach or suggest the claimed product " having improved dissolution and release rate properties" and "wherein substantially all of said norgestimate is in non-crystalline form and wherein said lactose stabilizes said norgestimate in its non-crystalline form", whether read singly or in combination.

In view of the foregoing, Appellants request that the Examiner's Final Rejection be overturned and that this application be passed to allowance at the earliest possible date.

Appellants believe that no fee is required under 37 C.F.R. § 41.20 for filing this Reply Brief. In the event a fee is required for filing this paper, please charge such fee, and any other fees that may be required, to Deposit Account No. 17-0750/ORT-1548/YPS.

Respectfully submitted,

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CLAIMS APPENDIX

1. An oral steroid hormone product having improved dissolution and release rate properties, said product comprising norgestimate in admixture with lactose, wherein substantially all of said norgestimate is in non-crystalline form and wherein said lactose stabilizes said norgestimate in its non-crystalline form.

6. The steroid hormone product of claim 1, wherein the product is one of an oral contraceptive product and a hormone replacement therapy product.

7. The steroid hormone product of claim 6, wherein the product is an oral contraceptive product comprising from about 10 μg to about 50 ug of an estrogen and/or from about 50 μg to about 300 μg of norgestimate.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None